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TITLE: Development and Evaluation of New Products for the Far-Forward Care of
Combat Casualties with Acute Lung Injury

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14. ABSTRACT OBJECTIVES: The principal objective for this phase of the study was to develop a new method of delivering chlorine gas for inhalation injury in sheep. Secondary objectives included the following: to assess the utility of the Suffolk breed of sheep for studies of inhalation injury; to demonstrate Optical Coherence Tomography (OCT) imaging of the trachea and bronchi following inhalation of chlorine, and to demonstrate Near-Infrared Diffuse Optical Spectroscopy (NIRS-DOS) monitoring of sheep following chlorine inhalation injury. HYPOTHESIS: Inhalation injury can be reliably produced by means of inhalation of chlorine gas by mechanical ventilation. RESULTS: Two hours following ventilation with 100 or 150 ppm chlorine in air, 300 liters total volume over 30 min, the mean±SD PaO ₂ -to-FiO ₂ ratio was 110±47, and the mean±SD survival time was 37±39 hrs. All animals developed acute respiratory distress syndrome (ARDS) by 2 hrs. after injury. Suffolk appeared to be more vulnerable to injury than the crossbred sheep previously used. OCT imaging showed minimal changes in the tracheal and bronchial mucosa and submucosa, consistent with the predominantly alveolar-capillary membrane level of this injury. NIRS-DOS showed decreases in tissue oxygen saturation (StO ₂) with injury. CONCLUSION: Delivery of chlorine by mechanical ventilation reliably caused ARDS in all animals studied. OCT was an excellent way to image the large airways non-invasively. NIRS-DOS enabled non invasive measurement of StO ₂ .					
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INTRODUCTION

This project represents a collaboration between the U.S. Army Institute of Surgical Research (ISR), Fort Sam Houston, TX, and the McGowan Institute of Regenerative Medicine at the University of Pittsburgh, Pittsburgh, PA. The goal is to improve our ability to treat casualties with acute respiratory distress syndrome (ARDS).

This is the final report on this grant. The reader is referred to previous publications and reports on the development and characterization of the chlorine ARDS model, and on experience with the Intravenous Membrane Oxygenator (IMO).

The work done during the past year was done on a no-cost extension to the protocol, and represents additional work done after completion of the main objectives of the original statement of work.

BODY

Regulatory Compliance

These studies were approved by the institutional Animal Care and Use Committee. The care of all animals was in accordance with the guidelines set forth by the Animal Welfare Act and other federal statutes and regulations relating to animals and studies involving animals, and by the 1996 *Guide for the Care and Use of Laboratory Animals* of the National Research Council. All animals were maintained in a facility approved by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Personnel and Training

Personnel involved in this study had accumulated considerable experience in rendering round-the-clock animal intensive care as reflected in previous reports. In 2006 Ms. C. Baird, Ms. D. Hardin, and SPC G. Rossman left the project. SPC H. Perry, Ms. M. Boehme-Lear, Dr. C. Moraru, and Mr. M. Lucas joined the project. Mr. Lucas had prior experience with Phase I of our project. New personnel received training during a series of studies on 9 sheep as part of ongoing studies.

MATERIALS AND METHODS

In 2006, we made three modifications to our study. The first was to change the breed of sheep to Suffolk to more closely emulate studies being performed at ALung Technologies. Second was a modification of the chlorine administration method in which a Siemens 900C ventilator was modified to administer chlorine. Lastly, we returned to the “dry” fluid management algorithm from our phase one studies, as volume loading appeared to have enhanced the injury in phase two.

Total sheep used for this study stands at 104. Fifty-two were used in model development and phase 1 studies. Twenty-three were used for multiple inert gas elimination technique (MIGET) studies. Twenty were used for phase 2 in crossbred sheep. Nine were used for the transition to Suffolk sheep and training of new personnel, i.e. during this reporting period.

Animal preparation

Certified non-pregnant female sheep were quarantined for one week. On the day of study, the animals were anesthetized with isoflurane and underwent placement of a urinary catheter, tracheostomy and lines in the right external jugular vein, right carotid artery, and left and right femoral arteries and veins. Enrofloxacin (Bayer, Shawnee Mission, Kansas, USA), 100 g/ml, 1 ml BID IM, was given as prophylaxis on the day of surgery and every 24 h. At completion of surgery isoflurane was tapered off, and total intravenous anesthesia (TIVA) was initiated (ketamine, 300-500 mcg/kg/min; midazolam, 1 mcg/kg/min) and continued throughout the experiment. Anesthesia levels were adjusted based on pinch tests and clinical assessment. When indicated, additional buprenorphine (Buprenex) 0.3 mg/kg IM was given for pain. The animals were transported to the ICU and mechanically ventilated (see Ventilator Management below).

General ICU care was similar to that reported previously, with the following exceptions. Fluid management followed the 4-2-1 rule. Supplemental fluids were not started until after 2-3 hours post injury and development of acute lung injury. No other fluids were administered. Lung-protective ventilation was used in this phase of the study. For details, see below.

Physiologic measurements

Arterial blood gases were measured every 6 hours with more frequent blood gas measurements as needed to ensure proper ventilator adjustments. A point-of-care analyzer was used (i-STAT portable clinical analyzer, #06F16-02; CG8+ cartridges, #220400; Abbot Laboratories, East Windsor, NJ).

A pulmonary arterial (PA) catheter (Thermodilution Catheter, Torque-line, 7 F, 4-lumen, #41239-04-05, Abbott Laboratories, North Chicago, IL) was inserted via the right external jugular introducer. Arterial and venous catheters were kept patent with heparin, 40 units/ml, 2-6 ml/flush. Pressures were transduced (Transpac IV trifurcated monitoring kit, #42650-06, Abbott Critical Care Systems, North Chicago, IL) with the transducers

level with the sheep's phlebostatic axis. The electrocardiogram, the pulse oximetry plethysmogram, and the central venous, pulmonary arterial, and systemic arterial blood pressure waveforms were continuously displayed using a Hewlett Packard clinical monitor (Model 88 M1176A).

At baseline, immediately after injury, and every 6 hours, the EKG and blood pressure waveforms were acquired at 500Hz to the DREW data acquisition system developed at ISR (Millar Instruments, Houston, TX). The cardiac output was determined by thermodilution, and the pulmonary capillary wedge pressure was measured.

Cl₂ injury

Inhalation injury occurred in a dedicated suite under negative-pressure conditions. Ambient sampling was used (detector head GM-PS-6A-H; sensor GM-CDS-6-CL10-R; Matheson Tri Gas, Chicago, IL) to detect gas leaks (none occurred). Personnel performing Cl₂ delivery wore full-face fitted gas masks. Custom gas mixtures consisting of Cl₂ (either 100 or 150 ppm) in medical air were used (Matheson Tri Gas). Cl₂ was delivered via tracheostomy.

In 2006, the gas administration system was modified by removing the flow transducer component of the system, and placing a Siemens 900C Ventilator without the blender to the 2nd stage of the pressure regulator on the pre-blended gas cylinder. Ventilator settings were based upon the animals' weight and maintaining an equivalent volume-based dose as was seen in phases 1 and 2. Tidal volume settings ranged from 10 to 12 cc/kg animal body weight. Respiratory rates were established by dividing the total dose of 300 liters (at 10 liters per minute) by the tidal volume in liters and establishing the number of breaths per minute required to deliver that volume.

The animal was exposed to chlorine gas for 30 minutes with arterial blood gases drawn at a minimum of twice during gas administration. The last blood gas was drawn at five minutes prior to the end of the chlorine administration. Expired air was passed through a Boeringer scavenger to a charcoal canister (Precision Filtration Products, Pennsburg, PA), and was evacuated via the institutional vacuum system. After exposure to Cl₂, the animals were transported back into the OR and monitored.

ICU management post-injury

TIVA was carried out during the study rendering the subjects unconscious throughout the duration of the protocol. When the MAP decreased below 50 mmHg despite resuscitation, dopamine was initiated at a rate of 2 mcg/kg/min. Over the duration of the study the rate was adjusted up to 20mcg/kg/min. When necessary, diuretics (furosemide and mannitol in one case) were used to stimulate urine output. Animals that developed decreased HR and/or bradycardia (HR < 60 beats/min) received antiarrhythmic interventions that included boluses of atropine, lidocaine and isoproterenol at standard recommended doses that were regulated by the attending veterinarian.

Fluid management

In this phase of the experiment we adopted the “dry” management fluid management algorithm used by us previously in Phase 1 of this project. This is because of our experience with the vigorous fluid loading after chlorine injury, which was associated with worsening pulmonary function. Thus, in this portion of the study urine output was maintained according to the 4-2-1 rule (4 ml/kg for the first 10 kg of body weight, 2 ml/kg for the next 10 kg, and 1 ml/kg for each additional kg). Supplemental fluids were not started until after 2-3 hours after injury. The maintenance i.v. fluids included 5% dextrose in water (D5W) at one-half the maintenance rate, plus normal saline (NS) at one-half the maintenance rate. Additional NS was given to maintain a urine output of 0.5 to 1 ml/kg/h. If the hourly urine output was less than 0.5 ml/kg/h, the NS was increased by 25%. If the hourly urine output was more than 1 ml/kg/h, the NS was decreased by 25%. The NS was not decreased below the maintenance rate. The D5W was adjusted only to treat hyponatremia or hypernatremia, which were rare. For these infusions, a dual channel volumetric infusion pump (Alaris Signature Gold IVAC, #7230) was used.

Ventilator management

A Servo 300-A (Siemens-Elementia, Sweden) mechanical ventilator was used. Volume control mode was used with 5 cm H₂O positive end expiratory pressure (PEEP). The fraction of inspired O₂ concentration was 21% and was adjusted as necessary to maintain SpO₂ ≥ 90% and partial pressure of O₂ in arterial blood (PaO₂) > 60 mm Hg.

After completion of the chlorine injury and arrival of the animal in the ICU, lung protective ventilation was initiated. According to this approach, the target for peak inspiratory pressure (PIP) was $PIP \leq 30$ cm H₂O. This was achieved by changing the tidal volume in 2 ml/kg steps down to a minimum of 6 ml/kg. With tidal volume (TV) changes, respiratory rate was also changed in an attempt to match the previous minute ventilation settings. If necessary, PaCO₂ was allowed to rise (permissive hypercapnia), and the pH was allowed to decrease to ≥ 7.15. If arterial pH was below 7.15, a high PIP was accepted.

IMO insertion

No IMOs were inserted in this portion of the study.

Experiment termination, necropsy

Ninety-six hours after injury or sooner in the event of imminent death [MAP <30 mm Hg for 30 min], animals were euthanized by an overdose of sodium pentobarbital (Fatal-Plus, Dearborn, MI). Dorsal sections of the middle lobe in the right lung were harvested, fixed in formalin and processed for H & E staining and light microscopical examination.

Optical Coherence Tomography (OCT)

In conjunction with the Beckman Laser Institute, we utilized new technology for imaging the airway that can provide near-histological resolution. The OCT was coupled to a bronchoscope and inserted into the airway of chlorine-injured sheep to various depths. Images were collected, and compared to histological sections from the same location. We imaged the posterior surface of the trachea just above the carina (1-2 cm above) as well as the posterior surface of the right main bronchus 5-8 cm deep from the carina. Four animals were imaged in this manner.

Diffuse Optical Spectroscopy (DOS)

Again in conjunction with the Beckman Laser Institute, we tested a device, Near-Infrared Diffuse Optical Spectroscopy (NIR-DOS), which non-invasively assesses tissue oxygenation. Spectral measurements were acquired at baseline, post-chlorine administration, post-dopamine administration, and post-chest tube insertion.

NIR-DOS employs frequency-domain photon migration analysis (FDPM). This allows independent measurements of tissue absorption and scattering properties at depths of 1 cm or more below the skin surface. The absorption properties of tissue provide the ability to determine absolute concentrations of deoxygenated hemoglobin (Hb-R), oxygenated hemoglobin (Hb-O₂), and water, as well as the total hemoglobin saturation (S_tO₂) for the region measured. The unique aspect of this technology developed at the UC Irvine Beckman Laser Institute is the ability to differentiate optical scattering from absorption (a problem that limited prior NIR technologies in the past). Four animals were studied with this system.

RESULTS

During the past year we encountered considerable difficulty in procuring Suffolk sheep due to an overall shortage and a lengthy mating season during which ewes were not obtainable. A total of 9 Suffolk sheep were utilized during the past year. Two animals had pre-existing pulmonary conditions, one had intubation trauma, and all three were excluded. One animal had an injury so severe that it was euthanized shortly after exposure. One animal received a sham injury, and ran the course of study.

In general, the Suffolk breed of sheep seemed to be more sensitive to the chlorine injury and the experimental conditions. Being a difficult breed to acquire, and having the sensitivities observed (more prone to peripheral edema due to body position, prone to development of metabolic acidosis due to salivary losses) this breed will be discontinued in future studies.

The use of the ventilator produced an injury that, on CT scan, was more centrally located. The injury was most prominent in and around the major airways at 2 hours. This is expected because lower tidal volumes were used: around 10 ml/kg vs. the previous method of forceful manual lung inflation with 13-15ml/kg tidal volumes. However, as seen in Table 1, the injury was nonetheless clinically significant as all of the animals subjected to injury developed severe ARDS (PaO₂-to-FiO₂ ratio, PFR<200).

Date	Animal number	Injury dose	PFR, 2 hrs. after injury	Survival time, hrs.
8-Aug-06	950	150 ppm Chlorine	100	5.3
29-Aug-06	937	150 ppm Chlorine	128	3.0
16-Oct-06	901	intubation injury	N/A excluded	N/A
23-Oct-06	932	150 ppm Chlorine	91	2.6
13-Nov-06	5	100 ppm Chlorine	198	68
28-Nov-06	4	100 ppm Chlorine	73	49
		preexisting pulmonary		
4-Dec-06	2	problem	N/A excluded	N/A
5-Dec-06	7	sham	333	96
11-Dec-06	1	100 ppm Chlorine	74	92
Mean±SD,				
injured animals	--	--	110±47	37±39

Optical Coherence Tomography (OCT)

The OCT is a minimally invasive optical device that can produce images of adjacent tissue at or near the resolution seen in histological samples. While histological analysis is still in progress, initial data suggest that the OCT images correlate well with histological assessment of injury and edema (Fig. 1 and 2). In these animals, OCT images of the large airways were unimpressive with respect to severity of injury. This is consistent with our previous findings, that the alveolar-capillary membrane injury following

chlorine gas inhalation is more prominent than the large airway injury. This is in contrast to smoke inhalation injury, in which the opposite is true.

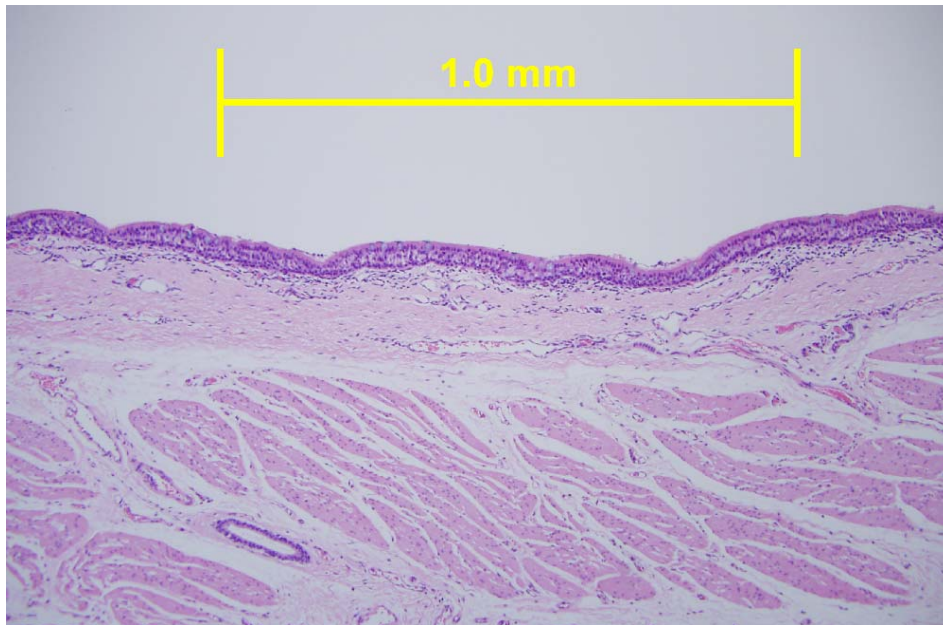


Figure 1. Histopathology, trachea, following chlorine inhalation injury (H and E).

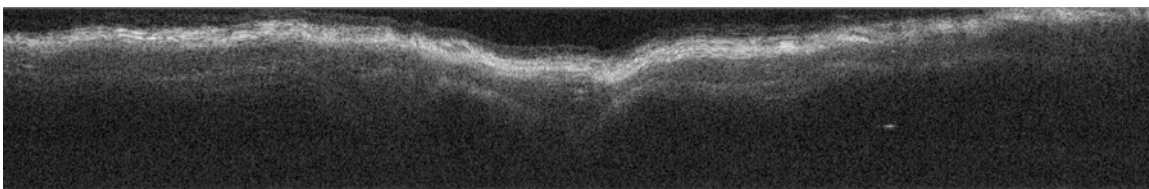


Figure 2. Optical coherence tomography scan of trachea following chlorine inhalation injury.

Diffuse Optical Spectroscopy (DOS)

As predicted, chlorine injury, by reducing blood pressure and peripheral tissue perfusion, resulted in a concomitant decrease in both oxyhemoglobin and total hemoglobin content (THC) as measured by the DOS. Conversely, conditions which increase blood pressure (dopamine administration) and placement of a chest tube due to a pneumothorax serve to increase the values of these parameters and were documented in our experiments. Figures 3 and 4 show levels of oxy-, deoxy- and total muscle (right thigh) hemoglobin concentration at baseline (ventilation with room air, 21% oxygen concentration) and in response to chlorine inhalation, dopamine administration and placement of a tube thoracostomy.

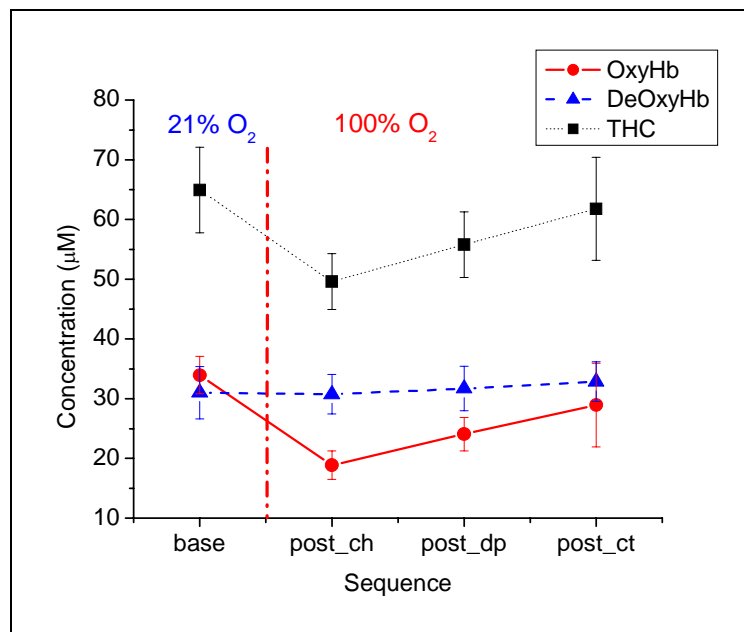


Fig. 3 Oxyhemoglobin (OxyHb), deoxyhemoglobin (DeOxyHb), and total hemoglobin (THC) concentration: Average of 3 locations at baseline (base), post chlorine injury (post_ch), post dopamine administration (post_dp), and after chest tube placement (post_ct)

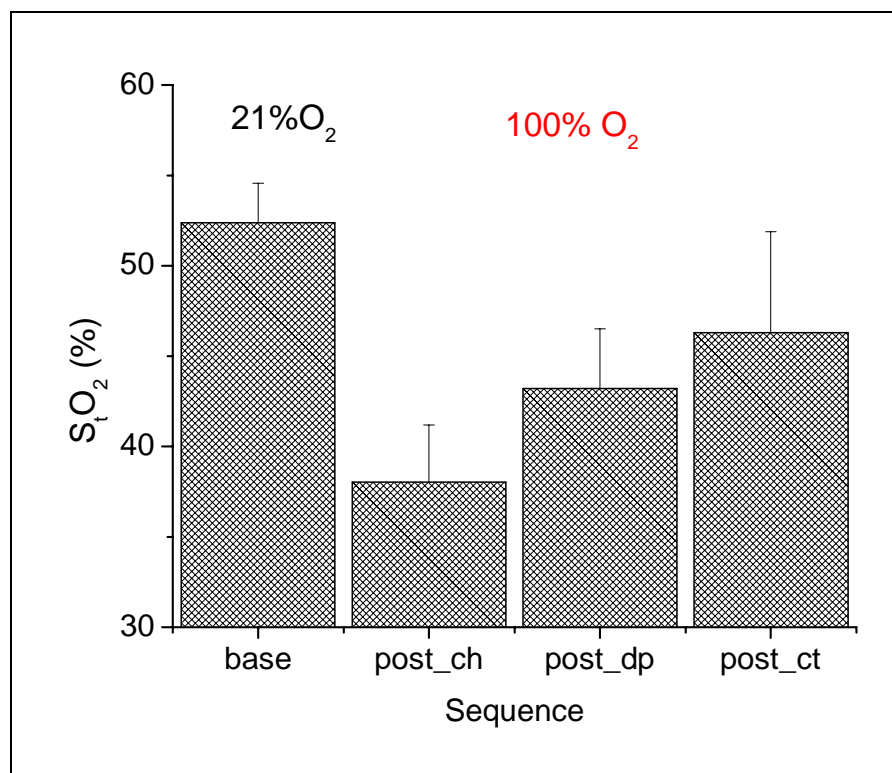


Fig. 4. Tissue saturation of oxygen by DOS (StO₂): Average of 3 locations at baseline, post chlorine injury, post dopamine administration, and after chest tube placement

This demonstrates the effectiveness of the DOS as a non-invasive assessment device in determining perfusion status in compromised individuals.

DISCUSSION

The principal findings of this portion of the study were:

- 1) Chlorine injury administration via the ventilator (a new delivery method) produced a clinically significant injury that led to severe lung injury and ARDS consistent with our previous work. This was manifested by the low PaO_2 -to- FiO_2 ratio (PFR) values in all animals subjected to chlorine injury ($\text{PFR} < 200$ at 2-3 hours post injury). Thus, administration of chlorine injury via a ventilator is feasible and produces ARDS.
- 2) Optical Coherence Tomography (OCT) constitutes an easily obtainable and minimally invasive method suitable for rapid imaging of the proximal airway.
- 3) Near-Infrared Diffuse Optical Spectroscopy (NIRS-DOS) is a minimally invasive method of monitoring for changes in peripheral tissue oxygenation due to acute lung injury and changes in hemodynamics.
- 4) Suffolk sheep are more vulnerable to this injury and/or study conditions, which makes this breed less suitable for use in our model.

This model will now be transitioned to swine. This is being done for the following reasons. First, sheep were an attractive model for this injury because experience at other labs suggests that sheep tolerate conscious mechanical ventilation well. However, our experience was that sheep do not tolerate mechanical ventilation well when they become hypoxic, and thus require heavy sedation or anesthesia. Thus, a potential advantage of sheep over other large animals is lost. Second, swine are available in larger quantities to us than are sheep. Third, the care of anesthetized ruminants over many days becomes difficult, because cessation of rumination and loss of fluids via the mouth cause metabolic acidosis, and because there are no established regimens for enteral nutrition (tube feeding).

Using other funding, we will continue evaluating both the IMO and a novel extracorporeal gas exchange device, the Paracorporeal Respiratory Assist Lung (Hemolung, ALung Technologies Inc., Pittsburgh, PA; <http://www.alung.com/hemolung.html>). These studies will begin in July 2007.

KEY RESEARCH ACCOMPLISHMENTS

The key research accomplishments for this year were:

- Transfer of manual chlorine injury delivery to a method using a mechanical ventilator.
- Performance of Optical Coherence Tomography (OCT) imaging of the trachea and bronchi following acute lung injury.
- Demonstration of a new method of near infrared spectroscopy (NIR-DOS) for monitoring of peripheral tissue oxygenation during acute lung injury and changes in hemodynamic status.
- Exclusion of Suffolk sheep from future studies involving inhalation injury and mechanical ventilation.

REPORTABLE OUTCOMES

Peer-Reviewed Publications (Cancio and Batchinsky, 2006-7):

(We have included all of our publications since the last report, whether directly related to lung injury or not.)

1. Batchinsky AI, Weiss WB, Jordan BS, Dick EJ Jr., Cancelada DA, Cancio LC. Ventilation-perfusion relationships following experimental pulmonary contusion. J Appl Physiol 2007 (in press).
2. White CE, Park MS, Renz EM, Kim SH, Schrank AE, Wolf SE, Cancio LC. Burn center treatment of patients with severe anhydrous ammonia injury: case reports and literature review. J Burn Care Research 2007 (in press).
3. Batchinsky AI, Cooke WH, Kuusela, TA, Jordan BS, Cancio LC. Sympathetic nerve activity and heart rate variability during severe hemorrhagic shock in sheep. Autonomic Neuroscience: Basic and Clinical 2007 (in press).
4. Schofield CM, Murray CK, Horvath EE, Cancio LC, Kim SH, Wolf SE, Hospenthal DR. Correlation of culture with histopathology in fungal burn wound colonization and infection. Burns 2007 (in press).
5. Murray CK, Hoffmaster RM, Schmit DR, Hospenthal DR, Ward JA, Cancio LC, Wolf SE. Evaluation of elevated temperature, white blood cell count, and neutrophil percentage as predictors of bloodstream infection in burn ICU patients. Arch Surg 2007 (in press).
6. Horvath EE, Murray CK, Vaughan GM, Hospenthal DR, Wade CE, Holcomb JB, Wolf SE, Mason AD Jr., Cancio LC. Fungal wound infection (not colonization) is independently associated with mortality in burn patients. Ann Surg 2007 (in press).
7. Cancio LC, Batchinsky AI, Dubick MA, Park MS, Black IH, Gómez R, Faulkner JA, Pfannenstiel TJ, Wolf SE. Inhalation injury: pathophysiology and clinical care. Burns 2007 (in press).
8. Cancio LC, Kuwa T, Matsui K, Drew GA, Galvez E Jr., Sandoval LL, Jordan BS. Intestinal and gastric tonometry during experimental burn shock. Burns 2007 (in press).
9. Gómez R, Cancio LC. Management of burn wounds in the Emergency Department. Emerg Med Clin N Am 2007;25:135-46.

10. Batchinsky AI, Cooke WH, Kuusela T, **Cancio** LC. Loss of complexity characterizes the heart-rate response to experimental hemorrhagic shock in swine. Crit Care Med 2007; 35(2):519-25.
11. **Cancio** LC, Kramer GC, Hoskins SL. Gastrointestinal fluid resuscitation of thermally injured patients. J Burn Care Research 2006;27:561-9.
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16. **Cancio** LC, Batchinsky AI, Mansfield JR, Panasyuk S, Hetz K, Martini D, Jordan BS, Tracey B, Freeman JE. Hyperspectral imaging: a new approach to the diagnosis of hemorrhagic shock. J Trauma 2006;60:1087-95.
17. Kuwa T, Jordan BS, **Cancio** LC. Use of power Doppler ultrasound to monitor renal perfusion during burn shock. Burns 2006; 32:706-13.
18. **Cancio** LC, Galvez E, Turner CE, Kypreos NG, Parker A, Holcomb JB. Base deficit and alveolar-arterial gradient during resuscitation contribute independently but modestly to the prediction of postburn mortality. J Burn Care Research 2006;27:289-97.
19. Batchinsky AI, Martini DK, Jordan BS, Dick EJ, Fudge J, Baird CA, Hardin DE, **Cancio** LC. Acute respiratory distress syndrome secondary to inhalation of chlorine gas in sheep. J Trauma. 2006;60:944-957.
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21. Kauvar DS, Cancio LC, Wolf SE, Wade CE, Holcomb JB. Comparison of combat and non-combat burns from ongoing U.S. military operations. J Surg Res 2006; 132:195-200.
22. Cancio LC, Galvez E, Jordan BS, Allies WE. Delivery of nitric oxide by high-frequency percussive ventilation: system design and evaluation. Clinical Intensive Care 2006;17:41-8.

Other publications, 2006-7

1. Cancio LC. Non-operative management of military abdominal trauma? J Trauma 2007 (in press).
2. Cancio LC. Book review: *The British Military Surgery Pocket Book*. J Trauma 2007 (in press).
3. Walters TJ, Holcomb JB, Cancio LC, Beekley AC, Baer DG. Emergency tourniquets. J Am Coll Surgeons 2007;204:185-6

CONCLUSIONS

We established an automated chlorine injury delivery mechanism using a ventilator which mimics physiologic breathing more closely and thus may be a more realistic mode of injury delivery suitable for future studies in ARDS. Noninvasive diagnosis of proximal airway injury via OCT and minimally invasive monitoring of peripheral tissue oxygen delivery deficits via NIRS-DOS are feasible and promising tools in acute lung injury.

Experience with the IMO catheter (summarized in previous reports) revealed that it is fairly easy to insert and operate. Aggressive fluid management resulted, however, in a worsening of pulmonary function in chlorine-injured animals, whose alveolar-capillary membrane injury evidently makes them vulnerable to pulmonary edema.

Future work with the IMO in swine will avoid volume loading. In addition, an extracorporeal device, the Paracorporeal Respiratory Assist Lung (PRAL), has also been developed at the University of Pittsburgh and will be compared to the IMO at this Institute.

The PRAL is similar to arteriovenous CO₂ removal (AVCO₂R) devices such as the Interventional Lung Assist (ILA, Novalung). In contrast to these devices, however, no arterial cannulation is required. Rather, a single dual-lumen catheter is inserted intravenously into the right atrium. Veno-venous flow is enabled by a rotating fiber bundle, which both propels blood and enhances gas exchange. During this fiscal year, testing of the PRAL in uninjured sheep began at ALung with surgical support by Dr. Batchinsky. This device will now be tested at the U.S. Army Institute of Surgical Research in injured animals in late 2007.

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